Hepatic Impairment:

- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. SEROQUEL is not approved for elderly patients with dementia-related psychosis (5.1)

Suicidal Thoughts and Behaviors

- Increased risk of suicidal thoughts and behavior in children, adolescents, and young adults taking antidepressants (5.2)
- Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)

---

**Recent Major Changes**

Warnings and Precautions, Falls (5.8)

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**Indications and Usage**

SEROQUEL is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia (1.1)
- Bipolar I disorder manic episodes (1.2)
- Bipolar disorder, depressive episodes (1.2)

---

**Dosage and Administration**

- SEROQUEL can be taken with or without food (2.1)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial Dose</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia - Adults (2.2)</td>
<td>25 mg twice daily</td>
<td>150-750 mg/day</td>
<td>750 mg/day</td>
</tr>
<tr>
<td>Schizophrenia - Adolescents (13-17 years) (2.2)</td>
<td>25 mg twice daily</td>
<td>400-800 mg/day</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Bipolar Mania - Adults Monotherapy or as an adjunct to lithium or divalproex (2.2)</td>
<td>50 mg twice daily</td>
<td>400 to 800 mg/day</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Bipolar Mania - Children and Adolescents (10 to 17 years), Monotherapy (2.2)</td>
<td>25 mg twice daily</td>
<td>400-600 mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Bipolar Depression - Adults (2.2)</td>
<td>50 mg once daily at bedtime</td>
<td>300 mg/day</td>
<td>300 mg/day</td>
</tr>
</tbody>
</table>

- Geriatric Use: Consider a lower starting dose (50 mg/day), slower titration, and careful monitoring during the initial dosing period in the elderly (2.3, 8.5)
- Hepatic Impairment: Lower starting dose (25 mg/day) and slower titration may be needed (2.4, 8.7, 12.3)

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**Dosage Forms and Strengths**

Tablets: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg (3)

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**Contraindications**

Known hypersensitivity to SEROQUEL or any components in the formulation. (4)

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**Warnings and Precautions**

- Cerebrovascular Adverse Reactions: Increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs (5.3)
- Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring (5.4)
- Metabolic Changes: Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5)
  - Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes
  - Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of treatment, and periodically, during treatment
- Weight Gain: Gain in body weight has been observed; clinical monitoring of weight is recommended
  - Tardive Dyskinesia: Discontinue if clinically appropriate (5.6)
- Hypotension: Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)
- Increased Blood Pressure in Children and Adolescents: Monitor blood pressure at the beginning of treatment and periodically during treatment in children and adolescents (5.9)
- Leukopenia, Neutropenia and Agranulocytosis: Monitor complete blood count frequently during the first few months of treatment in patients with a pre-existing low white blood cell count or a history of leukopenia/neutropenia and discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors (5.10)
- Cataracts: Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment (5.11)

---

**Adverse Reactions**

- Most common adverse reactions (incidence ≥5% and twice placebo): Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, dyspepsia (6.1)
- Children and Adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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**Drug Interactions**

- Concomitant use of strong CYP3A4 inhibitors: Reduce quetiapine dose to one sixth when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) (2.5, 7.1, 12.3)
- Concomitant use of strong CYP3A4 inducers: Increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7-14 days) of potent CYP3A4 inducers (e.g., phenytoin, ritampin, St. John’s wort) (2.6, 7.1, 12.3)
- Discontinuation of strong CYP3A4 inducers: Reduce quetiapine dose by 5 fold within 7-14 days of discontinuation of CYP3A4 inducers (2.6, 7.1, 12.3)

---

**Use in Specific Populations**

- Pregnancy: Limited human data. Based on animal data, may cause fetal harm. Quetiapine should be used only if the potential benefit justifies the potential risk (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother’s health (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide
**INDICATIONS AND USAGE**

**1.1 Schizophrenia**

SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents (13-17 years). The effectiveness of SEROQUEL for the maintenance treatment of schizophrenia has not been systematically evaluated in controlled clinical trials [see Clinical Studies (14.1)].

**1.2 Bipolar Disorder**

SEROQUEL is indicated for the acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. Efficacy was established in two 12-week monotherapy trials in adults, in one 3-week adjunctive trial in adults, and in one 3-week monotherapy trial in pediatric patients (10-17 years) [see Clinical Studies (14.2)].

SEROQUEL is indicated as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder. Efficacy was established in two 8-week monotherapy trials in adult patients with bipolar I and bipolar II disorder [see Clinical Studies (14.2)].

SEROQUEL is indicated for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex. Efficacy was established in two maintenance trials in adults. The effectiveness of SEROQUEL as monotherapy for the maintenance treatment of bipolar disorder has not been systematically evaluated in controlled clinical trials [see Clinical Studies (14.2)].

**1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder**

Pediatric schizophrenia and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Important Administration Instructions**

SEROQUEL can be taken with or without food.

**2.2 Recommended Dosing**

The recommended initial dose, titration, dose range and maximum SEROQUEL dose for each approved indication is displayed in Table 1. After initial dosing, adjustments can be made upwards or downwards, if necessary, depending upon the clinical response and tolerability of the patient [see Clinical Studies (14.1 and 14.2)].
2.6 Dose Modifications when used with CYP3A4 Inducers

SEROQUEL dose should be increased up to 5-fold of the original dose when used in combination with a chronic treatment (e.g., greater than 7-14 days) of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, or asavalim). The dose should be titrated based on the clinical response and tolerability of the individual patient. When the CYP3A4 inducer is discontinued, the dose of SEROQUEL should be reduced to the original level within 7-14 days [see Clinical Pharmacology (12.3) and Drug Interactions (7.1)].

2.7 Re-initiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address re-initiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL for less than one week, gradual dose escalation may not be required and the maintenance dose may be re-initiated.

2.8 Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be more appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

3 DOSAGE FORMS AND STRENGTHS

- 25 mg tablets are peach, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘25’ on one side and plain on the other side.
- 50 mg tablets are white, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘50’ on one side and plain on the other side.
- 100 mg tablets are yellow, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘100’ on one side and plain on the other side.
- 200 mg tablets are white, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘200’ on one side and plain on the other side.
- 400 mg tablets are yellow, capsule-shaped, biconvex, film coated tablets, intagliated with ‘SEROQUEL’ on one side and ‘300’ on the other side.
- 600 mg tablets are yellow, capsule-shaped, biconvex, film coated tablets, intagliated with ‘SEROQUEL’ on one side and ‘400’ on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to quetiapine or to any excipients in the SEROQUEL formulation. Anaphylactic reactions have been reported in patients treated with SEROQUEL.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analysis of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic of the patients is not clear. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic of the patients is not clear. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

Table 1: Recommended Dosing for SEROQUEL

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial Dose and Titration</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia-Adults</td>
<td>Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.</td>
<td>150-750 mg/day</td>
<td>750 mg/day</td>
</tr>
<tr>
<td>Schizophrenia-Adolescents (13-17 years)</td>
<td>Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.</td>
<td>400-800 mg/day</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Bipolar Mania-Adults Monotherapy</td>
<td>Day 1: Twice daily dosing totaling 100 mg. Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg. Day 4: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.</td>
<td>400-800 mg/day</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Bipolar Mania-Children and Adolescents (10 to 17 years) Monotherapy</td>
<td>Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 400 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day. Based on response and tolerability, may be administered three times daily.</td>
<td>400-600 mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Bipolar Depression-Adults</td>
<td>Administer once daily at bedtime. Day 1: 50 mg. Day 2: 100 mg. Day 3: 200 mg. Day 4: 300 mg.</td>
<td>300 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Bipolar I Disorder Maintenance Therapy-Adults</td>
<td>Administer twice daily totaling 400-800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized.</td>
<td>400-800 mg/day</td>
<td>800 mg/day</td>
</tr>
</tbody>
</table>

1. N/A Not applicable

Maintenance Treatment for Schizophrenia and Bipolar I Disorder

Maintenance Treatment – Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [see Clinical Studies (14.2)].

2.3 Dose Modifications in Elderly Patients

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [see Clinical Pharmacology (12.3) and Drug Interactions (7.1)]. When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on SEROQUEL 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the clinical response and tolerability of the individual patient.

2.4 Dose Modifications in Hepatically Impaired Patients

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased in increments of 25 mg/day - 50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

2.5 Dose Modifications when used with CYP3A4 Inhibitors

SEROQUEL dose should be reduced to one sixth of original dose when co-medicated with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc.). When the CYP3A4 inhibitor is discontinued, the dose of SEROQUEL should be increased by 50% [see Clinical Pharmacology (12.3) and Drug Interactions (7.1)].
No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.

Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients (including SEROQUEL patients with depressive symptoms) should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

5.3 Cerbrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. SEROQUEL is not approved for the treatment of patients with dementia-related psychosis [see also Boxed Warning and Warnings and Precautions (5.1)].

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose, and lipids was observed in clinical studies. Changes in these metabolic profiles should be managed as clinically appropriate.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoadiposis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia/diabetes mellitus should not be considered established. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia/diabetes-related adverse reactions in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Adults:

Table 3: Fasting Glucose – Proportion of Patients Shifting to >126 mg/dL in Short-Term (<12 weeks) Placebo-Controlled Studies

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Category Change (At Least Once) from Baseline</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose</td>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>Quetiapine</td>
<td>2907</td>
<td>71 (2.4%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>1346</td>
<td>19 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>Borderline to High (&lt;100 mg/dL and ≥126 mg/dL to ≥126 mg/dL)</td>
<td>Quetiapine</td>
<td>572</td>
<td>67 (11.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>279</td>
<td>33 (11.8%)</td>
<td></td>
</tr>
</tbody>
</table>

1. Includes SEROQUEL and SEROQUEL XR data.

In a 24-week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level ≥ 200 mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2-hour glucose from baseline was -1.8 mg/dL for quetiapine.

In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar I disorder maintenance, mean exposure of 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 mg/dL for SEROQUEL and -0.05 mg/dL for placebo. The exposure-adjusted rate of any increased glucose level (≥126 mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been precluded from calorie intake from fluids during fasting period) was 18.0 per 100 patient years for SEROQUEL (10.7% of patients; n=556) and 9.5 for placebo per 100 patient years (4.8% of patients; n=581).

Children and Adolescents:

In a placebo-controlled SEROQUEL monotherapy study of adolescent patients (13-17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for SEROQUEL (n=138) compared to placebo (n=67) was -0.75 mg/dL, versus –1.70 mg/dL. In a placebo-controlled SEROQUEL monotherapy study of children and adolescents patients (10-17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for SEROQUEL (n=170) compared to placebo (n=81) was 3.62 mg/dL versus –1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (≤100 mg/dL) had a baseline borderline fasting glucose level (>100 mg/dL and <126 mg/dL) that had a treatment-emergent blood glucose level of ≥126 mg/dL.

In a placebo-controlled SEROQUEL XR monotherapy study (8 weeks duration) of children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy...
was not established, the mean change in fasting glucose levels for SEROQUEL XR (n = 60) compared to placebo (n = 62) was 1.8 mg/dL versus 1.6 mg/dL. In this study, there were no patients in the SEROQUEL XR or placebo-treated groups with a baseline normal fasting glucose level (< 100 mg/dL) that had an increase in blood glucose level > 126 mg/dL. There was one patient in the SEROQUEL XR group with a baseline borderline fasting glucose level (≥ 130 mg/dL and < 126 mg/dL) who had an increase in blood glucose level of > 126 mg/dL compared to zero patients in the placebo group.

Dyslipidemia

Adults:

Table 4 shows the percentage of adult patients with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline by indication in clinical trials with SEROQUEL.

Table 4: Percentage of Adult Patients with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels by Indication

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Indication</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol ≥240 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 137 24 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Depression</td>
<td>Placebo 92 6 (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥200 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 120 26 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Depression</td>
<td>Placebo 70 11 (16%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-Cholesterol ≥160 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL na* na*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Depression</td>
<td>Placebo na* na*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol ≤40 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 393 56 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Depression</td>
<td>Placebo 214 29 (14%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 6 weeks duration
2. 8 weeks duration
3. Parameters not measured in the SEROQUEL registration studies for schizophrenia. Lipid parameters also were not measured in the bipolar mania registration studies.

Children and Adolescents:

Table 5 shows the percentage of children and adolescents with changes in total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol from baseline in clinical trials with SEROQUEL.

Table 5: Percentage of Children and Adolescents with Changes in Total Cholesterol, Triglycerides, LDL-Cholesterol and HDL-Cholesterol from Baseline to Clinically Significant Levels

<table>
<thead>
<tr>
<th>Laboratory Analyte</th>
<th>Indication</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol ≥200 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 107 13 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Placebo 56 1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 159 16 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Placebo 66 2 (3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-Cholesterol ≥130 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 103 17 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Placebo 51 4 (8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-Cholesterol ≤40 mg/dL</td>
<td>Schizophrenia</td>
<td>SEROQUEL 80 8 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Placebo 60 1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 13-17 years, 6 weeks duration
2. 10-17 years, 3 weeks duration

In a placebo-controlled SEROQUEL XR monotherapy study (8 weeks duration) of children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the percentage of children and adolescents with shifts in total cholesterol was 13% (2/83) for SEROQUEL XR vs. 3% (6/194) for placebo; triglycerides 15% (2/13) for SEROQUEL XR vs. 15% (2/13) for placebo; and LDL-cholesterol 13% (2/16) for SEROQUEL XR vs. 8% (1/13) for placebo.

Weight Gain

Increases in weight have been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight.

Children: In clinical trials with SEROQUEL, the following increases in weight have been reported.

Table 6: Proportion of Patients with Weight Gain ≥7% of Body Weight (Adults)

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Indication</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>SEROQUEL 391 18 (23%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania (monotherapy)</td>
<td>SEROQUEL 299 13 (13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania (adjunct therapy)</td>
<td>Placebo 196 8 (4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Depression</td>
<td>Placebo 554 14 (8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. up to 6 weeks duration
2. up to 12 weeks duration
3. up to 3 weeks duration
4. up to 8 weeks duration

The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and -0.4 kg in the placebo group. In the bipolar mania trial, which was 1.7 kg in the SEROQUEL group and 0.4 kg in the placebo group.

Children and Adolescents:

Table 7: Proportion of Patients with Weight Gain ≥7% of Body Weight (Children and Adolescents)

<table>
<thead>
<tr>
<th>Vital Sign</th>
<th>Indication</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Patients n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>SEROQUEL 111 23 (21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar Mania</td>
<td>Placebo 44 6 (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo 157 18 (12%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo 68 0 (0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. 6 weeks duration
2. 3 weeks duration

The mean change in body weight in the schizophrenia trial was 2.0 kg in the SEROQUEL group and 0.4 kg in the placebo group.

5.6 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including quetiapine. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon relapse estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should...
SEROQUEL® (quetiapine fumarate) Tablets

5.7 Hypotension

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-escalation period, probably reflecting its α-adrenergic antagonist properties. Syncope was reported in 1% (29/2858) for placebo; the incidence of increases at any time in diastolic blood pressure (≥30 mm Hg) was 6.2% (136/2135) for SEROQUEL and 2.1% (40/1853) for placebo. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg twice daily [see Dosage and Administration (2.2)]. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

5.8 Falls

Atypical antipsychotic drugs, including SEROQUEL, may cause somnolence, postural hypotension, akinesia or akineti...tauromegalony and myoclonus. For patients with concomitant illness, and those who are over 65 years old or who have a history of falls or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Increases in Blood Pressure (Children and Adolescents)

In placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure (≥20 mm Hg) was 15.2% (51/335) for SEROQUEL and 5.5% (9/163) for placebo; the incidence of increases at any time in diastolic blood pressure (≥10 mm Hg) was 40.6% (136/335) for SEROQUEL and 24.5% (40/163) for placebo. In the 26-week open-label clinical trial, one child with a reported history of hypertension experienced a hypertensive crisis.

5.10 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue SEROQUEL and have their WBC followed until recovery.

5.13 Seizures

During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics, SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.14 Hypothyroidism

Adults: Clinical trials with quetiapine demonstrated dose-related increases in thyroid hormone levels. The reduction in total and free thyroid hormone (T4) of approximately 20% at the higher end of the therapeutic dose range was maximal in the first six weeks of treatment and maintained without adaptation or progression during more chronic therapy. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. The mechanism by which quetiapine affects the thyroid axis is unclear. If there is an effect on the hypothalamic-pituitary axis, measurement of TSH alone may not accurately reflect a patient’s thyroid status. Therefore, hypothyroidism and free T4 levels in addition to clinical assessment, should be measured at baseline and at follow-up.

In the manic adjunctive studies, where SEROQUEL was added to lithium or divalproex, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo-treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels (free T4 <0.8 LLN).

About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Some patients with TSH increases needed replacement thyroid treatment.

In all quetiapine trials, the incidence of significant shifts in thyroid hormones and TSH were 0% (0/39) for placebo (free T<0.8 LLN), 2.0% (35/17513); decrease in total T4, 4.0% (71/17513); decrease in total T4, 0.4% (53/13766); increase in free T4, 0.7% (51/6707); increase in total T4, 4.0% (75/1861); increase in free T4, 0.9% (47/5200); increase in TSH, 4.9% (556/11941). In eight patients, where TSH was measured, levels of T4 were unchanged.

Table 8 shows the incidence of these shifts in short-term placebo-controlled clinical trials.

Table 8: Incidence of Shifts in Thyroid Hormone Levels and TSH in Short-Term Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Shift</th>
<th>Total T4</th>
<th>Free T4</th>
<th>Total T3</th>
<th>Free T3</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEROQUEL Placebo</td>
<td>3.4%</td>
<td>0.6%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Placebo Placebo</td>
<td>0.7%</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total</td>
<td>4.1%</td>
<td>0.7%</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Placebo Placebo</td>
<td>0.7%</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

1. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline. Shifts in total T4, free T4, total T3 and free T3 are defined as <0.8 x LLN (pmol/L), and shift in TSH is both TSH and free T4 at any time. TSH at any time.
2. Includes SEROQUEL and SEROQUEL XR data.

In short-term placebo-controlled monotherapy trials, the incidence of reciprocal, shifts in T4 and TSH was 0.0% for both quetiapine (1/4800) and placebo (0/2190) and for T4 and TSH the shifts were 0.1% (7/6154) for quetiapine versus 0.0% (1/3007) for placebo.

Children and Adolescents: In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts for thyroid function values at any time for SEROQUEL treated patients and placebo-treated patients for TSH was 2.9% (8/270) vs. 0.7% (1/138), respectively, and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145), respectively. Of the SEROQUEL treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

5.15 Hyperprolactinemia

Adults: During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a significantly clinically important value occurred in 3.6% (158/4161) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

Children and Adolescents: In acute placebo-controlled trials in children and adolescent patients with bipolar mania (3-week duration) or schizophrenia (6-week duration), the incidence of shifts in prolactin levels to a significantly clinically important value (≥20 μg/L) was 13.4% (18/134) for SEROQUEL compared to 0.4% (2/527) on active control drugs. Orthostatic hypotension, dizziness, and syncope can lead to falls. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Table 8 shows the incidence of these shifts in short-term placebo-controlled clinical trials.

Shifts in total T4, free T4, total T3 and free T3 are defined as ≥0.8 x LLN (pmol/L), and shift in TSH is both TSH and free T4 at any time.

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2. Includes SEROQUEL and SEROQUEL XR data.

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Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, glycosuria and/or impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds that elevate prolactin levels, mammary adenocarcinomas, pituitary and pancreatic adenomas were observed in carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive [see Nonclinical Toxicology (13.1)].

5.16 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose titration. In schizophrenia trials, somnolence was reported in 18% (89/510) of patients on SEROQUEL compared to 11% (22/206) of placebo patients. In acute bipolamia trials using SEROQUEL as monotherapy, somnolence was reported in 16% (34/209) of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar manic trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% (66/198) of patients on SEROQUEL compared to 5% (19/393) of placebo patients. In bipolar depression trials, somnolence was reported in 57% (398/698) of patients on SEROQUEL compared to 15% (51/347) of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. Somnolence may lead to falls.

5.17 Body Temperature Regulation

Although not reported with SEROQUEL, disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic drugs. Appropriate care is advised when patients with a known heat sensitive disorder undergoing treatment with SEROQUEL are exposed to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

5.18 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.19 Discontinuation Syndrome

Acute withdrawal symptoms, such as insomnia, nausea, and vomiting have been described after abrupt cessation of typical antipsychotic drugs, including SEROQUEL. In short-term placebo-controlled, monotherapy clinical trials with SEROQUEL XR that included a discontinuation phase which evaluated discontinuation symptoms, the aggregated incidence of patients experiencing one or more discontinuation symptoms after abrupt cessation was 12.1% (6/50) for SEROQUEL XR and 6.7% (7/106) for placebo. The incidence of the individual adverse events (i.e., insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved after 1 week post-discontinuation. Gradual withdrawal is advised.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.13)].
- Suicidal thoughts and behaviors in adolescents and young adults [see Warnings and Precautions (5.2)].
- Cerebrovascular adverse reactions, including stroke in elderly patients with dementia-related psychosis [see Warnings and Precautions (5.3)].
- Neuroleptic Malignant Syndrome (NMS) [see Warnings and Precautions (5.4)].
- Metabolic changes (hyperglycemia, dyslipidemia, weight gain) [see Warnings and Precautions (5.5)].
- Tardive dyskinesia [see Warnings and Precautions (5.6)].
- Hypotension [see Warnings and Precautions (5.7)].
- Falls [see Warnings and Precautions (5.8)].
- Increases in blood pressure (children and adolescents) [see Warnings and Precautions (5.9)].
- Leukopenia, neutropenia and agranulocytosis [see Warnings and Precautions (5.10)].
- Cataracts [see Warnings and Precautions (5.11)].
- QT Prolongation [see Warnings and Precautions (5.12)].
- Cardiac Disorders [see Warnings and Precautions (5.13)].
- Hypothyroidism [see Warnings and Precautions (5.14)].
- Hyperprolactinemia [see Warnings and Precautions (5.15)].
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.16)].
- Body temperature regulation [see Warnings and Precautions (5.17)].
- Dysphagia [see Warnings and Precautions (5.18)].
- Discontinuation Syndrome [see Warnings and Precautions (5.19)].

6.1 Clinical Study Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adults:

The information below is derived from a clinical trial database for SEROQUEL consisting of over 4300 patients. This database includes 638 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy), 646 patients exposed to SEROQUEL for the maintenance treatment of bipolar I disorder as adjunct therapy, and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 4300 subjects, approximately 4000 (2300 in schizophrenia, 405 in acute bipolar mania, 638 in bipolar depression, and 846 for the maintenance treatment of bipolar I disorder) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 2400 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) double-blind phases of short-term, placebo-controlled efficacy studies, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed.

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse reactions (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials.

Bipolar Disorder: Mania: Overall, discontinuations due to adverse reactions were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

Depression: Overall, discontinuations due to adverse reactions were 12.3% for SEROQUEL vs. 10.0% for SEROQUEL 600 mg and 5.2% for placebo.

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials:

In the acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) trials, the most commonly observed adverse reactions associated with the use of SEROQUEL monotherapy (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (5%), ALT increased (5%), weight gain (5%), and dyspepsia (5%).

Adverse Reactions Occurring at an Incidence of 2% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials:
The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population as a whole.

Table 9 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 2% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 9: Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (Monotherapy)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL (n=719)</th>
<th>PLACtOE (n=404)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>21%</td>
<td>14%</td>
</tr>
<tr>
<td>Agitation</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>18%</td>
<td>8%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Constipation</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Itch</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>AST Increased</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Fever</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>
In the acute adjunct therapy of bipolar mania (up to 3 weeks) studies, the most commonly observed adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Table 11 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during therapy (up to 3 weeks) of acute mania in 2% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 10: Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL (n=196)</th>
<th>PLACEBO (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>34%</td>
<td>9%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>Headache</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>6%</td>
</tr>
<tr>
<td>Tremor</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Postural Hypotension</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Agitation</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertonia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Twitching</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Depression</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Amblyopia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Speech Disorder</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hormone Level Altered</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Heaviness</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Fever</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Incoordination</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Thinking Abnormal</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Sweating</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

In bipolar depression studies (up to 8 weeks), the most commonly observed treatment emergent adverse reactions associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (75%), dry mouth (44%), dizziness (18%), constipation (10%), and lethargy (5%).

Table 11 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during therapy (up to 8 weeks) of acute mania in 2% or more of patients treated with SEROQUEL (doses ranging from 300 to 600 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 11: Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL (n=698)</th>
<th>PLACEBO (n=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>57%</td>
<td>15%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>44%</td>
<td>13%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Orthostatic Hypotension</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Cough</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Irritability</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Sinus Congestion</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Tremor</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Gastroesophageal Reflux Disease</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Balance Disorder</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1. Somnolence combines adverse reaction terms somnolence and sedation.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Reactions: Spontaneously elicited adverse reaction data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse reactions. Logistic regression analyses revealed a positive dose response (p<0.05) for the following adverse reactions: dyspepsia, abdominal pain, and weight gain.

Adverse Reactions in clinical trials with quetiapine and not listed elsewhere in the label:

The following adverse reactions have also been reported with quetiapine: nightmares, hypersensitivity and elevations in serum creatine phosphokinase (not associated with NMS), galactorrhea, bradycardia (which may occur at or near initiation of treatment and be associated with hypotension and/or syncope) decreased platelets, somnambulism (and other related events), elevations in gamma-GT levels, hypothermia, and priapism.

Extrapyramidal Symptoms (EPS):

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with higher potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Four methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates Parkinsonism and akathisia, (2) Barnes Akathisia Rating Scale (BARS) Global Assessment Score, (3) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypotonia, hypokinesia, neck rigidity, and tremor), and (4) use of anticholinergic medications to treat emergent EPS.

Adults: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates Parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity,
The following findings were based on a 6-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 800 mg/day. The incidence of discontinuation due to adverse reactions for quetiapine was greater than the incidence in placebo-treated patients.

In bipolar mania therapy (up to 3 weeks) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (33%), dizziness (18%), fatigue (11%), increased appetite (9%), nausea (8%), vomiting (8%), tachycardia (7%), dry mouth (7%), and weight increased (6%).

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 6 weeks) of schizophrenia in 2% or more of patients treated with SEROQUEL (doses of 400 or 800 mg/day) where the incidence in patients treated with SEROQUEL was at least twice the incidence in placebo-treated patients.

In an acute (8-week) SEROQUEL XR trial in children and adolescents (10-17 years of age) with bipolar depression, in which efficacy was not established, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater and at least twice that for placebo) were dizziness (7%), fatigue (5%), nausea (5%), and constipation (4%).

**Table 12: Adverse Reactions Associated with EPS in a Short-Term, Placebo-Controlled Multiple Fixed-Dose Phase III Schizophrenia Trial (6 weeks duration)**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL 75 mg/day (N=53)</th>
<th>SEROQUEL 150 mg/day (N=48)</th>
<th>SEROQUEL 300 mg/day (N=52)</th>
<th>SEROQUEL 600 mg/day (N=51)</th>
<th>SEROQUEL 800 mg/day (N=51)</th>
<th>Placebo (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td>n %</td>
</tr>
<tr>
<td>Dystonic event</td>
<td>2.3</td>
<td>2.4</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>2.3</td>
<td>3.0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3.6</td>
</tr>
<tr>
<td>Akathisia</td>
<td>1</td>
<td>1.9</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>Dyskinetic event</td>
<td>3.8</td>
<td>3.8</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>Other extrapyramidal event</td>
<td>2.3</td>
<td>3.0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Parkinsonism incidence rates as measured by the Simpson-Angus total score for placebo and the five fixed doses (75, 150, 300, 600, 750 mg/day) were: -0.6 to -1.2 to -1.6 to -1.8 and -1.8. The rate of anticholinergic medication use to treat emergent EPS for placebo and the five fixed doses was: 14% to 11% to 10% to 12% and 11%.

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse reactions potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse reactions (akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups.

**Table 13: Adverse Reaction Incidence in a 6-Week Placebo-Controlled Clinical Trial for the Treatment of Schizophrenia in Adolescent Patients**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL 400 mg (n=72)</th>
<th>SEROQUEL 800 mg (n=74)</th>
<th>Placebo (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>33%</td>
<td>35%</td>
<td>11%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>4%</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6%</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Irritability</td>
<td>3%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>1%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Epigastric</td>
<td>3%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Tooth Abscess</td>
<td>3%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thirst</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1. Somnolence combines adverse reaction terms somnolence and sedation.
2. Tachycardia combines adverse reaction terms tachycardia and sinus tachycardia.

**Table 14: Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania in Children and Adolescent Patients**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL 400 mg (n=95)</th>
<th>SEROQUEL 600 mg (n=96)</th>
<th>Placebo (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>50%</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19%</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>10%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>6%</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>7%</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>3%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>6%</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>Irritability</td>
<td>3%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Aggression</td>
<td>1%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Musculoskeletal Stiffness</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Accidental Overdose</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Acne</td>
<td>3%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Pallor</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Stomatoh Dyscomfort</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Syncope</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>5%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Constipation</td>
<td>4%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Ear Pain</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Peristhesia</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Sinus Congestion</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thirst</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

1. Somnolence combines adverse reaction terms somnolence and sedation.
2. Tachycardia combines adverse reaction terms tachycardia and sinus tachycardia.
Extrapyramidal Symptoms:
In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% (19/147) for SEROQUEL and 5.3% (4/75) for placebo, though the incidence of the individual adverse drug reactions (extrapyramidal symptoms, akathisia, restless legs, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% (7/193) or SEROQUEL and 1.1% (1/90) for placebo.

Table 15 presents a listing of patients with adverse reactions potentially associated with extrapyramidal symptoms in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration). In Tables 15–16 dystonic event included nuchal rigidity, hyperpnea, and muscle rigidity; parkinsonism included cogwheel rigidity and tremor; akathisia included akathisia only; dyskinesia event included tardive dyskinesia, dyskinesia, and choreoathetosis; and other extrapyramidal event included restlessness and extrapyramidal disorder.

Table 16: Adverse Reactions Associated with Extrapyramidal Symptoms in a Placebo-Controlled Trial in Adolescent Patients with Schizophrenia (6-week duration).

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL 400 mg/day (N=95)</th>
<th>SEROQUEL 800 mg/day (N=98)</th>
<th>All SEROQUEL (N=193)</th>
<th>Placebo (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonic event</td>
<td>2 1.1 1.0</td>
<td>2 1.1 1.0</td>
<td>2 1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>4 5.5 4.5</td>
<td>4 5.4</td>
<td>3 3.6</td>
<td>2 2.2</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3 4.1 4.5</td>
<td>7 8.4</td>
<td>5 4.4</td>
<td>3 4.0</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>2 2.7 0.0</td>
<td>2 1.4</td>
<td>1 0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other Extrapyramidal event</td>
<td>2 2.7</td>
<td>2 2.4</td>
<td>2 2.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 16 presents a listing of patients with adverse reactions associated with extrapyramidal symptoms in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration).

Table 17: Adverse Reactions Associated with Extrapyramidal Symptoms in a Placebo-Controlled Trial in Children and Adolescent Patients with Bipolar I Mania (3-week duration).

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>SEROQUEL 400 mg/day (N=95)</th>
<th>SEROQUEL 600 mg/day (N=98)</th>
<th>All SEROQUEL (N=193)</th>
<th>Placebo (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonic event</td>
<td>2 1.1 1.0</td>
<td>2 1.1 1.0</td>
<td>2 1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>4 5.5 4.5</td>
<td>4 5.4</td>
<td>3 3.6</td>
<td>2 2.2</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3 4.1 4.5</td>
<td>7 8.4</td>
<td>5 4.4</td>
<td>3 4.0</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>2 2.7 0.0</td>
<td>2 1.4</td>
<td>1 0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other Extrapyramidal event</td>
<td>2 2.7</td>
<td>2 2.4</td>
<td>2 2.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1. There were no adverse experiences with the preferred term of dystonic or dyskinetic events.

Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL
Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 400 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, or those for which the relationship to SEROQUEL therapy was judged to be remote.

Cardiovascular System: Intrequent: vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; Rare: angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T-wave flattening; ST abnormality, increased GRS duration.

Respiratory System: Frequent: cough increased, dyspnea, Intrequent: pneumonia, epistaxis, asthma; Rare: hiccup, hyperventilation.

Metabolic and Nutritional System: Intrequent: weight loss, alkaline phosphatase increased, hyperlipidemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; Rare: glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: Intrequent: pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; Rare: exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: Intrequent: dysmenorrhea, vaginitis, urinary incontinence, megalourethra, uterine polyp, uterine fibromyoma; Rare: vaginal moniliasis, abnormal ejaculation, cystitis, urinary frequency, amenorrhea, female lactation, leukorrhea, vaginal hemorrhage, vulvovaginitis, orchitis; Rare: gynecomastia, nocturia, polyuria, acute kidney failure.

Special Senses: Intrequent: conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; Rare: abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: Intrequent: pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: Intrequent: leukocytosis, anemia, ecchymosis, eosinophilia, hyperbilirubinemia, anemia; Rare: lymphadenopathy, cyanosis, thrombocytopenia.

Endocrine System: Intrequent: hyperthyroidism, diabetes mellitus; Rare: hyperthyroidism.

Laboratory, ECG and vital sign changes observed in clinical studies
Laboratory Changes:
Neutrophil Counts
Adults: In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count <1.0 x 10^9/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine fumarate, compared to 0.1% (2/1949) in patients treated with placebo [see Warnings and Precautions (5.10)].

Transaminase Elevations
Adults: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT and AST) have been reported. In schizophrenic trials in adults, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% (29/483) for SEROQUEL compared to 1% (3/3194) for placebo. In acute bipolar mania trials in adults, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL (3/560) and placebo (3/3294). These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in two 6-week placebo-controlled trials was 1% (5/598) for SEROQUEL and 2% (8/497) for placebo.

Decreased Hemoglobin
Adults: In short-term placebo-controlled trials, decreases in hemoglobin to ≤ 13 g/dL males, ≤ 12 g/dL females on at least one occasion occurred in 8.3% (594/7155) of quetiapine-treated patients.

Other Adverse Reactions Observed During the Pre-Marketing Evaluation of SEROQUEL
Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, and those reaction terms which were so general as to be uninformative. It is important to emphasize that, although the reactions reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

Nervous System: Intrequent: abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased; urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, cataleptic reaction, hemiplegia; Rare: aphasia, baccoglossal syndrome, choreoathetosis, delirium, emotional liability, euphoria, libido decreased; neuromatosis, stuttering, subdural hematoma.

Body as a Whole: Frequent: flu syndrome; Intrequent: neck pain, pelvic pain; Rare: suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; Abdomen enlarged.

Digestive System: Intrequent: anorexia; Intrequent: increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, facial incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; Rare: glossitis, hematemesis, intestinal obstruction, melema, pancreatitis.
Children and Adolescents: In the acute (6 week) schizophrenia trial in adolescents, increases in heart rate (> 110 bpm) occurred in 5.2% (3/73) of patients receiving SEROQUEL 400 mg and 8.5% (5/57) of patients receiving SEROQUEL 800 mg compared to 0% (0/75) of patients receiving placebo. Mean increases in heart rate were 3.8 bpm and 11.2 bpm for SEROQUEL 400 mg and 800 mg groups, respectively, compared to a decrease of 3.3 bpm in the placebo group [see Warnings and Precautions (5.7)].

In the acute (3 week) bipolar mania trial in children and adolescents, increases in heart rate (> 110 bpm) occurred in 1.1% (1/89) of patients receiving SEROQUEL 400 mg and 4.7% (4/85) of patients receiving SEROQUEL 600 mg compared to 0% (0/86) of patients receiving placebo. Mean increases in heart rate were 12.8 bpm and 13.4 bpm for SEROQUEL 400 mg and 600 mg groups, respectively, compared to a decrease of 1.7 bpm in the placebo group [see Warnings and Precautions (5.7)].

In an acute (8-week) SEROQUEL XR trial in children and adolescents (10-17 years of age) with bipolar depression, in which efficacy was not established, increases in heart rate (> 110 bpm 10-12 years and 13-17 years) occurred in 0% of patients receiving SEROQUEL XR and 1.2% of patients receiving placebo. Mean increases in heart rate were 3.4 bpm for SEROQUEL XR, compared to 0.3 bpm in the placebo group [see Warnings and Precautions (5.7)].

6.2 Postmarketing Experience

The following adverse reactions were identified during post approval of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported since market introduction which were temporally related to quetiapine therapy include anaphylactic reaction, cardiomyopathy, drug reaction with eosinophilia and systemic symptoms (DRESS), hyponatremia, myocarditis, nocturnal enuresis, pancreatitis, retrograde amnesia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Drugs Interactions

7.1 Effect of Other Drugs on Quetiapine

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.

Adverse reactions reported since market introduction which were temporally related to quetiapine therapy include anaphylactic reaction, cardiomyopathy, drug reaction with eosinophilia and systemic symptoms (DRESS), hyponatremia, myocarditis, nocturnal enuresis, pancreatitis, retrograde amnesia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

8.1 Pregnancy

Pregnancy Category C: Risk Summary

There are no adequate and well-controlled studies of SEROQUEL use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy. In animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies, these postmarketing data do not reliably estimate the frequency or absence of adverse events. Neonates exposed to antipsychotic drugs (including SEROQUEL), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Animal Data

Pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no teratogenic effect at doses up to 2.4 times the maximum recommended human dose (MRHD) for schizophrenia of 800 mg/day based on mg/m² body surface area. However, there was evidence of embryo-fetal toxicity, which included delays in skeletal ossification occurring at approximately 1 and 2 times the MRHD of 800 mg/day in both rats and rabbits, and an increased incidence of cataractal (minor soft tissue anomaly) in rabbit fetuses at approximately 2 times the MRHD. In addition, fetal weight was decreased in both species.

Maternal toxicity (observed as decreased body weights and/or death) occurred at 2 times the MRHD in rats and approximately 1-2 times the MRHD (all doses tested) in rabbits.

In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.12, and 0.24 times the MRHD of 800 mg/day based on mg/m² body surface area. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3 times the MRHD.

8.2 Labor and Delivery

The effect of SEROQUEL on labor and delivery in humans is unknown.

8.3 Nursing Mothers

SEROQUEL was excreted into human milk. Because of the potential for serious adverse reactions in nursing infants from SEROQUEL, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother’s health.

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.06% to 0.43% of the weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal daily dose of 400 mg).

8.4 Pediatric Use

In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults.

Orthostatic hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (< 1%) [see Warnings and Precautions (5.7) and Adverse Reactions (6.1)].

Schizophrenia

The efficacy and safety of SEROQUEL in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one 6-week, double-blind, placebo-controlled trial [see Indications and Usage (1.1), Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.1)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 13 years of age with schizophrenia have not been established.

Maintenance

The safety and effectiveness of SEROQUEL in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of SEROQUEL in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.

Bipolar Mania

The efficacy and safety of SEROQUEL in the treatment of mania in children and adolescents ages 10-17 years with Bipolar I disorder was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial [see Indications and Usage (1.2), Dosage and Administration (2.3), Adverse Reactions (6.1), and Clinical Studies (14.2)].

Safety and effectiveness of SEROQUEL in pediatric patients less than 10 years of age with bipolar mania have not been established.

Bipolar Depression

Safety and effectiveness of SEROQUEL in pediatric patients less than 18 years of age with bipolar depression have not been established. A clinical trial with SEROQUEL XR was conducted in children and adolescents (10-17 years of age) with bipolar depression. Efficacy was not established.

Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10-17 years of age) and adults. When adjusted for weight, the AUC and Cmax of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight [see Clinical Pharmacology (12.3)].

8.5 Geriatric Use

Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to
SEROQUEL® (quetiapine fumarate) Tablets

SEROQUEL®, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients [see Clinical Pharmacology (12.3) and Dosage and Administration (3.2)].

8.6 Renal Impairment
Clinical experience with SEROQUEL in patients with renal impairment is limited [see Clinical Pharmacology (12.3)].

8.7 Hepatic Impairment
Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in patients with hepatic impairment. In this population, a low starting dose of 25 mg/day is recommended and the dose may be increased in increments of 25 mg/day - 50 mg/day [see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
SEROQUEL is not a controlled substance.

9.2 Abuse
SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL. e.g., development of tolerance, increases in dose, drug-seeking behavior.

10 OVERDOSAGE

10.1 Human Experience
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse reactions or recovered fully from the reported reactions. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug’s known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose [see Warnings and Precautions (5.12)]. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first-degree heart block. In post-marketing experience, there were cases reported of QT prolongation with overdose. There were also very rare reports of overdose of SEROQUEL alone resulting in death or coma.

10.2 Management of Overdosage
In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) might be additive to those of quetiapine, resulting in problematic hypotension. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of buphenyl might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

SEROQUEL® (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo [b,f]1,4-thiazepin-11-yl-1-piperazinyl[ethyl]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is C37H39N2O5S·C6H4O2 and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:

![Structural formula of quetiapine fumarate](image)

Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.

Inactive ingredients are povidone, dibasic di calcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg and 400 mg tablets contain only yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism of action of SEROQUEL is unknown. However, it has been proposed that the efficacy of SEROQUEL in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL’s antagonism of histamine H1 receptors may explain the somnolence observed with this drug.

SEROQUEL’s antagonism of adrenergic α1 receptors may explain the orthostatic hypotension observed with this drug.

12.2 Pharmacodynamics
SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5HT2 and 5HT1 receptors (IC50s=717 & 148nM, respectively), dopamine D1 and D2 (IC50s=1268 & 329nM, respectively), histamine H1 (IC50s=520nM), and adrenergic α1 and α2 receptors (IC50s=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC50s>5000 nM).

Effect on QT interval
In clinical trials quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post-marketing experience there were cases reported of QT prolongation in patients who overdosed on quetiapine [see Overdosage (10.1)], in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval.

12.3 Pharmacokinetics

Adults
Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Children and Adolescents
At steady state the pharmacokinetics of the parent compound, in children and adolescents (10–17 years of age), were similar to adults. However, when adjusted for dose and weight, AUC and Cmax of the parent compound were 41% and 39% lower, respectively, in children and adolescents than in adults. For the active metabolite, norquetiapine, AUC and Cmax were 45% and 31% higher, respectively, in children and adolescents than in adults. When adjusted for dose and weight, the pharmacokinetics of the metabolite, norquetiapine, was similar between children and adolescents and adults [see Use in Specific Populations (8.4)].

Absorption
Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with Cmax and AUC values increased by 25% and 15%, respectively.

Distribution
Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10-14 L/kg. It is 85% bound to plasma proteins at therapeutic concentrations. In vitro, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination
Following a single oral dose of 14C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulf oxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. In vitro studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulf oxide metabolite and in the metabolism of its active metabolite N-desalkyl quetiapine.

Age
Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary [see Dosage and Administration (2.9)].

Gender
There is no gender effect on the pharmacokinetics of quetiapine.
Race
There is no race effect on the pharmacokinetics of quetiapine.

Smoking
Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency
Patients with severe renal impairment (CrCl=10-30 mL/min/1.73 m2, n=8) had a 25% lower mean oral clearance than normal subjects (CrCl= > 80 mL/min/1.73 m2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients [see Use in Specific Populations (8.6)].

Hepatic Insufficiency
Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and Cmax were 3 times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed [see Dosage and Administration (2.4) and Use in Specific Populations (8.7)].

Drug-Drug Interaction Studies
The in vivo assessments of effect of other drugs on the pharmacokinetics of quetiapine are summarized in Table 17 [see Dosage and Administration (2.5 and 2.6) and Drug Interactions (7.1)].

Table 17: The Effect of Other Drugs on the Pharmacokinetics of Quetiapine

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose Schedules</th>
<th>Quetiapine</th>
<th>Effect on quetiapine Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotoin</td>
<td>100 mg twice daily</td>
<td>250 mg three times daily</td>
<td>No effect on absorption or mean oral clearance</td>
</tr>
<tr>
<td>Divalproex</td>
<td>500 mg twice daily</td>
<td>150 mg three times daily</td>
<td>17% increase in mean max plasma concentration at steady state. No effect on absorption or mean oral clearance</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>200 mg twice daily</td>
<td>250 mg three times daily</td>
<td>84% decrease in oral clearance resulting in a 6.2 fold increase in AUC of quetiapine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>60 mg once daily</td>
<td>300 mg twice daily</td>
<td>No change in steady state PK</td>
</tr>
<tr>
<td>Impiramine</td>
<td>75 mg twice daily</td>
<td>300 mg three times daily</td>
<td>No change in steady state PK</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>7.5 mg twice daily</td>
<td>300 mg two times daily</td>
<td>No change in steady state PK</td>
</tr>
<tr>
<td>Risperidone</td>
<td>3mg twice daily</td>
<td>300 mg twice daily</td>
<td>No change in steady state PK</td>
</tr>
</tbody>
</table>

In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on in vivo metabolism mediated by cytochromes CYP 1A2, 2C9, 2C19, 2D6 and 3A4. Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (Table 18) [see Drug Interactions (7.2)].

Table 18: The Effect of Quetiapine on the Pharmacokinetics of Other Drugs

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose Schedules</th>
<th>Quetiapine</th>
<th>Effect on other drugs Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>2mg, single dose</td>
<td>25mg three times daily</td>
<td>Oral clearance of lorazepam reduced by 20%</td>
</tr>
<tr>
<td>Divalproex</td>
<td>500 mg twice daily</td>
<td>150 mg three times daily</td>
<td>Cmax and AUC of free valproic acid at steady-state was decreased by 10-12%</td>
</tr>
<tr>
<td>Lithium</td>
<td>Up to 2400 mg/day given in twice daily doses</td>
<td>250 mg three times daily</td>
<td>No effect on steady-state pharmacokinetics of lithium</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>1g, single dose</td>
<td>250 mg three times daily</td>
<td>No effect on clearance of antipyrine or urinary recovery of its metabolites</td>
</tr>
</tbody>
</table>

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Carcinogenicity studies were conducted in C57BL/6 mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (MRHD) of 800 mg/day based on mg/m² body surface area (mouse) or 0.3, 1, and 3 times the MRHD based on mg/m² body surface area (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses 1.5 and 4.5 times the MRHD on mg/m² body surface area and in male rats at a dose of 3 times the MRHD on mg/m² body surface area. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (0.3, 1, and 3 times the MRHD on mg/m² body surface area).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in males and females, respectively. Increases in bone marrow haemopoietic basophils have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown [see Warnings and Precautions (5.15)].

Mutagenesis
The mutagenic potential of quetiapine was tested in the in vitro Ames bacterial gene mutation assay and in vivo in vitro assays in Chinese hamster ovary cells. The clastogenic potential of quetiapine was tested in the in vitro chromosomal aberration assay in cultured human lymphocytes and in the in vivo bone marrow micronucleus assay in rats up to 500 mg/kg which is 6 times the maximum recommended human dose on mg/m² body surface area. Based on weight of evidence quetiapine was not mutagenic or clastogenic in these tests.

Impairment of Fertility
Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or approximately 1 and 3 times the maximum human dose (MRHD) of 800 mg/day on mg/m² body surface area. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 3 times the MRHD even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the MRHD on mg/m² body surface area. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose approximately 1 times the MRHD of 800 mg/day on mg/m² body surface area. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in luteal cycles was observed at doses of 10 and 50 mg/kg, or approximately 0.1 and 1 times the MRHD of 800 mg/day on mg/m² body surface area. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the MRHD of 800 mg/day on mg/m² body surface area.

13.2 Animal Toxicology and/or Pharmacology

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10 to 200 mg/kg in rats and 75 to 250 mg/kg in mice; these doses are 0.1-3, and 0.1-4.5 times the maximum recommended human dose (MRHD) of 800 mg/day on mg/m² body surface area, respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the MRHD of 800 mg/day on mg/m² body surface area. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose-related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the MRHD of 800 mg/day on mg/m² body surface area.

14 CLINICAL STUDIES

14.1 Schizophrenia

Short-term Trials-Adults
The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in none of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol. To provide a reliable and valid comparison of SEROQUEL and haloperidol, a single dose haloperidol arm was included as a comparative treatment in none of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.
The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) (study 1) involving 5 fixed doses of SEROQUEL (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day and 750 mg/day given in divided doses three times per day), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 mg/day to 750 mg/day were generally indistinguishable.

2. In a 6-week, placebo-controlled trial (n=286) (study 2) involving titration of SEROQUEL in high (up to 750 mg/day given in divided doses three times per day) and low (up to 250 mg/day given in divided doses three times per day) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score.

3. In a 6-week dose and dose regimen comparison trial (n=618) (study 3) involving two fixed doses of SEROQUEL (450 mg/day given in divided doses twice daily and three times daily and 50 mg/day given in divided doses twice daily), only the 450 mg/day (225 mg given twice daily) dose group was superior to the 50 mg/day (25 mg given twice daily) SEROQUEL group on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score.

The primary efficacy results of these three studies in the treatment of schizophrenia in adults is presented in Table 19.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 years compared to those older than 40. The clinical significance of this finding is unknown.

Adolescents (ages 13-17)
The efficacy of SEROQUEL in the treatment of schizophrenia in adolescents (13-17 years of age) was demonstrated in a 6-week, double-blind, placebo-controlled trial (study 4). Patients who met DSM-IV criteria for schizophrenia were randomized into one of three treatment groups: SEROQUEL 400 mg/day (n = 73), SEROQUEL 800 mg/day (n = 74), or placebo (n = 75).

Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day (divided and given two or three times per day). Subsequently, the dose was titrated to the target dose of 400 mg/day or 800 mg/day using increments of 100 mg/day, divided and given two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale (PANSS).

SEROQUEL at 400 mg/day and 800 mg/day was superior to placebo in the reduction of PANSS total score. The primary efficacy results of this study in the treatment of schizophrenia in adolescents is presented in Table 19.

Table 19: Schizophrenia Short-Term Trials

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Endpoint: BPRS Total</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>SEROQUEL (75 mg/day)</td>
<td>45.7 (10.9)</td>
<td>-2.2 (2.0)</td>
<td>-4.0 (-11.2, 3.3)</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>SEROQUEL (150 mg/day)</td>
<td>47.2 (10.1)</td>
<td>-8.7 (2.1)</td>
<td>-10.4 (-17.8, -3.0)</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>SEROQUEL (300 mg/day)</td>
<td>45.3 (10.9)</td>
<td>-8.6 (2.1)</td>
<td>-10.3 (-17.6, -3.0)</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>SEROQUEL (600 mg/day)</td>
<td>43.5 (11.3)</td>
<td>-7.7 (2.1)</td>
<td>-9.4 (-16.7, -2.1)</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>SEROQUEL (750 mg/day)</td>
<td>45.7 (11.0)</td>
<td>-6.3 (2.0)</td>
<td>-8.3 (-15.2, -0.8)</td>
<td></td>
</tr>
<tr>
<td>Study 6</td>
<td>Placebo</td>
<td>45.3 (9.2)</td>
<td>1.7 (2.1)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

In these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was the Youth Mania Rating Scale (YMRS), a 15-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/ thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy
The efficacy of SEROQUEL in the acute treatment of bipolar mania was established in 2 placebo-controlled trials. In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 mg/day and 800 mg per day (studies 1 and 2 in Table 20).

Adjunct Therapy
In this 3-week placebo-controlled trial, 170 patients with bipolar mania (YMRS ≥ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score (study 3 in Table 20).

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 mg/day and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

The primary efficacy results of these studies in the treatment of mania in adults is presented in Table 20.

Children and Adolescents (ages 10-17)
The efficacy of SEROQUEL in the acute treatment of manic episodes associated with bipolar disorder in children and adolescents (10-17 years of age) was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial (study 4 in Table 20). Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups: SEROQUEL 400 mg/day (n = 95), SEROQUEL 600 mg/day (n = 98), or placebo (n = 91).

Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day (divided doses given two or three times daily). Subsequently, the dose was titrated to a target dose of 400 mg/day or 600 mg/day using increments of 100 mg/day, divided doses two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale (PANSS).

SEROQUEL 400 mg/day and 600 mg/day were superior to placebo in the reduction of YMRS total score (Table 20).

Table 20: Mania Trials

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: YMRS Total</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>SEROQUEL (200-800 mg/day)</td>
<td>34.0 (6.1)</td>
<td>-12.3 (1.3)</td>
<td>-4.0 (-7.0, -1.0)</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>Placebo</td>
<td>32.0 (6.1)</td>
<td>-15.7 (1.3)</td>
<td>-7.4 (-10.4, -4.4)</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>Haloperidol</td>
<td>33.3 (7.1)</td>
<td>-15.2 (1.6)</td>
<td>-8.5 (-11.5, -5.5)</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>Placebo</td>
<td>34.0 (6.1)</td>
<td>-6.7 (1.6)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>Lithium</td>
<td>31.5 (6.8)</td>
<td>-13.8 (1.6)</td>
<td>-3.7 (-7.1, -0.6)</td>
<td></td>
</tr>
<tr>
<td>Study 6</td>
<td>Placebo + mood stabilizer</td>
<td>31.1 (5.5)</td>
<td>-10.1 (1.5)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 7</td>
<td>Placebo</td>
<td>28.4 (5.9)</td>
<td>-14.3 (0.96)</td>
<td>-5.2 (-8.1, -2.3)</td>
<td></td>
</tr>
<tr>
<td>Study 8</td>
<td>SEROQUEL (600 mg/day)</td>
<td>29.6 (6.4)</td>
<td>-15.6 (0.97)</td>
<td>-6.6 (-9.5, -3.7)</td>
<td></td>
</tr>
<tr>
<td>Study 9</td>
<td>Placebo</td>
<td>30.7 (5.9)</td>
<td>-9.0 (1.1)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

Mood stabilizer: lithium or divalproex; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

1. Doses that are statistically significantly superior to placebo.
2. Difference (drug minus placebo) in least-squares mean change from baseline.
3. Included in the trial as an active comparator.
4. Adult data mean baseline score is based on patients included in the primary analysis; pediatric mean baseline score is based on all patients in the ITT population.

Bipolar Disorder, Depressive Episodes

Adults
The efficacy of SEROQUEL for the acute treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed 8-week, randomized, double-blind, placebo-controlled studies (N=1045) (studies 5 and 6 in Table 21). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to SEROQUEL were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale.
with scores ranging from 0 to 60. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, SEROQUEL was superior to placebo in reduction of MADRS score. Improvement in symptoms, as measured by change in MADRS score relative to placebo, was seen in both studies at Day 8 (week 1) and onwards. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

The primary efficacy results of these studies in the acute treatment of depressive episodes associated with bipolar disorder in adults is presented in Table 21.

### Table 21: Depressive Episodes Associated with Bipolar Disorder

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: MADRS Total</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SEROQUEL (300 mg/day)</td>
<td></td>
<td>30.3 (5.0)</td>
<td>-16.4 (0.9)</td>
<td>-6.1 (-8.3, -3.9)</td>
</tr>
<tr>
<td>5</td>
<td>SEROQUEL (600 mg/day)</td>
<td></td>
<td>30.3 (5.3)</td>
<td>-16.7 (0.9)</td>
<td>-6.5 (-8.7, -4.3)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>30.6 (5.3)</td>
<td>-10.3 (0.9)</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>SEROQUEL (300 mg/day)</td>
<td></td>
<td>31.1 (5.7)</td>
<td>-16.9 (1.0)</td>
<td>-5.0 (-7.3, -2.7)</td>
</tr>
<tr>
<td></td>
<td>SEROQUEL (600 mg/day)</td>
<td></td>
<td>29.9 (5.6)</td>
<td>-16.0 (1.0)</td>
<td>-4.1 (-6.4, -1.8)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>29.6 (5.4)</td>
<td>-11.9 (1.0)</td>
<td>--</td>
</tr>
</tbody>
</table>

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
1. Doses that are statistically significantly superior to placebo.
2. Difference (drug minus placebo) in least-squares mean change from baseline.

### Maintenance Treatment as an Adjunct to Lithium or Divalproex

The efficacy of SEROQUEL in the maintenance treatment of bipolar I disorder was established in 2 placebo-controlled trials in patients (n=1329) who met DSM-IV criteria for bipolar I disorder (studies 7 and 8 in Figures 1 and 2). The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on SEROQUEL plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either SEROQUEL (administered twice daily totaling 400 mg/day to 800 mg/day) or placebo. Approximately 50% of the patients had discontinued from the SEROQUEL group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score ≥ 20 or MADRS score ≥ 20 at 2 consecutive assessments; or study discontinuation due to a mood event. (Figure 1 and Figure 2)

In both studies, SEROQUEL was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for increasing time to recurrence of both manic and depressed episodes. The effect of SEROQUEL was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

### Figure 1 Kaplan-Meier Curves of Time to Recurrence of A Mood Event (Study 7)

**Figure 2** Kaplan-Meier Curves of Time to Recurrence of A Mood Event (Study 8)

### 16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘25’ on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

50 mg Tablets (NDC 0310-0276) white, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘50’ on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with ‘SEROQUEL’ and ‘100’ on one side and plain on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with ‘SEROQUEL’ and ‘200’ on one side and plain on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with ‘SEROQUEL’ on one side and ‘300’ on the other side, are supplied in bottles of 60 tablets, and hospital unit dose packages of 100 tablets.

400 mg Tablets (NDC 0310-0279) yellow, capsule-shaped, biconvex, film coated tablets, intagliated with ‘SEROQUEL’ on one side and ‘400’ on the other side, are supplied in bottles of 100 tablets, and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

### 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines. Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Suicidal Thoughts and Behaviors

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.
Neuroleptic Malignant Syndrome (NMS)
Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [see Warnings and Precautions (5.4)].

Hyperglycemia and Diabetes Mellitus
Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [see Warnings and Precautions (5.5)].

Hyperlipidemia
Patients should be advised that elevations in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol may occur. Patients should have their lipid profile monitored at the beginning of and periodically during treatment [see Warnings and Precautions (5.5)].

Weight Gain
Patients should be advised that they may experience weight gain. Patients should have their weight monitored regularly [see Warnings and Precautions (5.5)].

Orthostatic Hypotension
Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls), especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [see Warnings and Precautions (5.7)].

Increased Blood Pressure in Children and Adolescents
Children and adolescent patients should have their blood pressure measured at the beginning of, and periodically during, treatment [see Warnings and Precautions (5.9)].

Leukopenia/Neutropenia
Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL [see Warnings and Precautions (5.10)].

Interference with Cognitive and Motor Performance
Patients should be advised of the risk of somnolence or sedation (which may lead to falls), especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely [see Warnings and Precautions (5.16)].

Heat Exposure and Dehydration
Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see Warnings and Precautions (5.17)].

Concomitant Medication
As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs [see Drug Interactions (7.1)].

Pregnancy and Nursing
Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with SEROQUEL [see Use in Specific Populations (8.1) and (8.3)].

Need for Comprehensive Treatment Program
SEROQUEL is indicated as an integral part of a total treatment program for adolescents with schizophrenia and pediatric bipolar disorder that may include other measures (psychological, educational, and social). Effectiveness and safety of SEROQUEL have not been established in pediatric patients less than 13 years of age for schizophrenia or less than 10 years of age for bipolar mania. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician’s assessment of the chronicity and severity of the patient’s symptoms [see Indications and Usage (1.3)].
SEROQUEL® (quetiapine fumarate) Tablets

Read this Medication Guide before you start taking SEROQUEL and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about SEROQUEL?

SEROQUEL may cause serious side effects, including:

1. risk of death in the elderly with dementia. Medicines like SEROQUEL can increase the risk of death in elderly people who have memory loss (dementia). SEROQUEL is not for treating psychosis in the elderly with dementia.

2. risk of suicidal thoughts or actions (antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions).
   - Talk to your or your family member’s healthcare provider about:
     - all risks and benefits of treatment with antidepressant medicines.
     - all treatment choices for depression or other serious mental illness
   - Antidepressant medications may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
   - Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or suicidal thoughts or actions.
   - How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
     - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
     - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
     - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Data from other antidepressants suggest that:

• acting aggressive, being angry, or violent
• acting on dangerous impulses
• an extreme increase in activity and talking (mania)
• other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

• Never stop an antidepressant medicine without first talking to your healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

• Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member take. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

• Not all antidepressant medicines prescribed for children are FDA approved for use in children. Talk to your child’s healthcare provider for more information.

What is SEROQUEL?

SEROQUEL is a prescription medicine used to treat:

• schizophrenia in people 13 years of age or older
• bipolar disorder in adults, including:
  - depressive episodes associated with bipolar disorder
  - manic episodes associated with bipolar I disorder alone or with lithium or divalproex
  - long-term treatment of bipolar I disorder with lithium or divalproex
• manic episodes associated with bipolar I disorder in children ages 10 to 17 years old

It is not known if SEROQUEL is safe and effective in children under 10 years of age.

What should I tell my healthcare provider before taking SEROQUEL?

Before you take SEROQUEL, tell your healthcare provider if you have or have had:

• diabetes or high blood sugar in you or your family. Your healthcare provider should check your blood sugar before you start SEROQUEL and also during therapy
• high levels of total cholesterol, triglycerides or LDL-cholesterol or low levels of HDL-cholesterol
• low or high blood pressure
• low white blood cell count
• cataracts
• seizures
• abnormal thyroid tests
• high prolactin levels
• heart problems

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

• thoughts about suicide or dying
• attempts to commit suicide
• new or worse depression
• new or worse anxiety
• feeling very agitated or restless
• panic attacks
• trouble sleeping (insomnia)
• new or worse irritability
• liver problems
• any other medical condition
• pregnancy or plans to become pregnant. It is not known if SEROQUEL will harm your unborn baby.
• Breast-feeding or plans to breast-feed. SEROQUEL can pass into your breast milk. You and your healthcare provider should decide if you will take SEROQUEL or breast-feed. You should not do both.

Tell the healthcare provider about all the medicines that you take or recently have taken including prescription medicines, over-the-counter medicines, herbal supplements and vitamins.

SEROQUEL and other medicines may affect each other causing serious side effects, SEROQUEL may affect the way other medicines work, and other medicines may affect how SEROQUEL works.

Tell your healthcare provider if you are taking SEROQUEL. SEROQUEL may affect how other medicines work, and other medicines may affect SEROQUEL and may cause serious side effects. SEROQUEL may affect the way other medicines work, and other medicines may affect how SEROQUEL works.

Tell your healthcare provider if you are having a urine drug screen because SEROQUEL may affect your test results. Tell those giving the test that you are taking SEROQUEL.

How should I take SEROQUEL?
• Take SEROQUEL exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
• Take SEROQUEL by mouth, with or without food.
• If you feel you need to stop SEROQUEL, talk with your healthcare provider first. If you suddenly stop taking SEROQUEL, you may have side effects such as trouble sleeping or trouble staying asleep (insomnia), nausea, and vomiting.
• If you miss a dose of SEROQUEL, take it as soon as you remember. If you are close to your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time unless your healthcare provider tells you to. If you are not sure about your dosing, call your healthcare provider.

What should I avoid while taking SEROQUEL?
• Do not drive, operate machinery, or do other dangerous activities until you know how SEROQUEL affects you. SEROQUEL may make you drowsy.
• Avoid getting overheated or dehydrated.
  ° Do not over-exercise.
  ° In hot weather, stay inside in a cool place if possible.
  ° Stay out of the sun. Do not wear too much or heavy clothing.
  ° Drink plenty of water.
• Do not drink alcohol while taking SEROQUEL. It may make some side effects of SEROQUEL worse.

What are possible side effects of SEROQUEL?
SEROQUEL can cause serious side effects, including:
• See “What is the most important information I should know about SEROQUEL?”
• stroke that can lead to death can happen in elderly people with dementia who take medicines like SEROQUEL
• neuroleptic malignant syndrome (NMS). NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including SEROQUEL. NMS can cause death and must be treated in a hospital. Call your healthcare provider right away if you become severely ill and have some or all of these symptoms:
  ° high fever
  ° excessive sweating
  ° rigid muscles
  ° confusion
  ° changes in your breathing, heartbeat, and blood pressure
• falls can happen in some people who take SEROQUEL. These falls may cause serious injuries.
• high blood sugar (hyperglycemia). High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:
  ° build up of acid in your blood due to ketones (ketoacidosis)
  ° coma
  ° death

Increases in blood sugar can happen in some people who take SEROQUEL. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes) your healthcare provider should check your blood sugar before you start SEROQUEL and during therapy.

Call your healthcare provider if you have any of these symptoms of high blood sugar (hyperglycemia) while taking SEROQUEL:
  ° feel very thirsty
  ° need to urinate more than usual
  ° feel very hungry
  ° feel weak or tired
  ° feel sick to your stomach
  ° feel confused, or your breath smells fruity
• high fat levels in your blood (increased cholesterol and triglycerides). High fat levels may happen in people treated with SEROQUEL. You may not have any symptoms, so your healthcare provider may decide to check your cholesterol and triglycerides during your treatment with SEROQUEL.
• increase in weight (weight gain). Weight gain is common in people who take SEROQUEL so you and your healthcare provider should check your weight regularly. Talk to your healthcare provider about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.
• movements you cannot control in your face, tongue, or other body parts (tardive dyskinesia). These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking SEROQUEL. Tardive dyskinesia may also start after you stop taking SEROQUEL.
• decreased blood pressure (orthostatic hypotension), including lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
• increases in blood pressure in children and teenagers. Your healthcare provider should check blood pressure in children and adolescents before starting SEROQUEL and during therapy.
• low white blood cell count
• cataracts
• seizures
• abnormal thyroid tests. Your healthcare provider may do blood tests to check your thyroid hormone level.
• increases in prolactin levels. Your healthcare provider may do blood tests to check your prolactin levels.
• sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities
• increased body temperature
• difficulty swallowing
• trouble sleeping or trouble staying asleep (insomnia), nausea, or vomiting if you suddenly stop taking SEROQUEL. These symptoms usually get better 1 week after you start having them.

The most common side effects of SEROQUEL include:

In Adults:
• dry mouth
• constipation
• dizziness
• sore throat
• weakness
• difficulty moving
• abdominal pain

In Children and Adolescents:
• nausea
• increased appetite
• dry mouth
• vomiting
• weight gain
• rapid heart beat

These are not all the possible side effects of SEROQUEL. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SEROQUEL?
• Store SEROQUEL at room temperature, between 68°F to 77°F (20°C to 25°C).
• Keep SEROQUEL and all medicines out of the reach of children.

General information about the safe and effective use of SEROQUEL
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SEROQUEL for a condition for which it was not prescribed. Do not give SEROQUEL to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about SEROQUEL. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SEROQUEL that is written for health professionals.

For more information, go to www.SEROQUEL.com, or call 1-800-236-9933.

What are the ingredients in SEROQUEL?
Active ingredient: quetiapine fumarate
Inactive ingredients: povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25 mg tablets contain red and yellow ferric oxide. The 100 mg and 400 mg tablets contain only yellow ferric oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.
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Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850
Revised: 02/2017 3331108 3/17